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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/460,186	06/02/1995	REID VON BORSTEL	1331-138	5103

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EXAMINER	
KHARE, DEVESH	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/460,186	VON BORSTEL ET AL.	
	Examiner	Art Unit	
	Devesh Khare	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's remarks filed on 09/21/2006 are acknowledged.

The examiner acknowledges the typographical error as the applicant pointed out. The "US 5,346,708" should be "US 5,246,708" and "US 8,060,459" should be "US 6,060,459".

The rejection under obviousness-type double patenting of the Office Action dated 03/21/2005 over U.S. patent nos. 5,736,531; 5,968,914; and 6,344,447 has been withdrawn in response to applicant's remarks that claims were restricted in the parent application. The rejection over U.S. patent nos. 6,258,795; 6,465,440; 6,472,378; 6,297,222; 6,054,441; and 5,770,582 has been withdrawn because claims are directed to certain compounds/compositions.

Claims 1-25 are currently pending in this application.

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over U.S. Patent No. 6,329,350 ('350) and applicant's other U.S. Patents of same scope as following:

5,246,708; 5,470,838; 5,583,117; 5,691,320; 6,020,320; 6,020,322; 6,060,459; 6,103,701; 6,232,298; 6,255,290; 6,274,563; 6,306,834; 6,316,426; 6,348,451; 6,403,565; 6,417,170; 6,743,782, of record.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '350 patent claims a method in claims 1-7 for treating cancer consisiting essentially of administering to an animal a therapeutically effective amount of a pyrimidine nucleotide precursor which is a pyrimidine nucleoside or prodrug thereof wherein said methods are encompassed by or has substantial overlap with the methods of the instant claims. The instant methods are drawn for preventing or treating toxicity due to a pyrimidine analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside.

Claims in U.S. Patent no. 5,691,320 are directed to methods for treating or preventing tissue damage; sepsis and for reducing the toxicity of a therapeutic cytokine or inflammatory stimulus; U.S. Patent no. 6,232,298 are directed to methods for treating cachexia; U.S. Patent no. 5,583,117 are directed to methods treating cardiac insufficiency and myocardial infarction; U.S. Patent no. 5,470,838 are directed to treating cardiac insufficiency, cirrhosis of the liver and myocardial infarction; U.S. patent no. 6,274,563 are directed to methods for treating diabetes; U.S. patent no. 6,316,426 are directed to methods for treating a central nervous system disorder; similarly claims of U.S. Patent nos. 6,403,565; 6,417,170; 6,020,322; 6,103,701; 6,306,834; 6,348,451; 6,060,459; 6,020,782; and 6,255,290 are directed to the method of treatment of certain other diseases. It is noted that the methods of treatment of various diseases set forth in

these patents are accomplished by the pyrimidine nucleoside or prodrug of close structural analogs used in the instant claims.

It would be obvious to select the pyrimidine nucleoside or prodrug thereof set forth in the claims of the issued patent for preventing or treating toxicity due to a pyrimidine analog of instant claims because the composition containing an acylated derivative of a non-methylated pyrimidine nucleoside would be considered an inherent property of the pyrimidine nucleosides for the treatment of cancer as well as preventing or treating toxicity due to a pyrimidine analog in an animal, absent any clear and convincing evidence and/or arguments to the contrary.

The molecule comprising pyrimidine nucleosides may well be varied in terms of its inherent activity, in this case to accomplish prevention or treatment of toxicity due to a pyrimidine analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside.

The examiner notes the instant claims; the '350 patent and all other U.S. Patents as set forth supra of applicants, claims do indeed substantially overlap because the method in the instant claims and the said patents are deemed same or substantial same and this obviousness-type double patenting rejection is necessary to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

Therefore the claims are co-extensive.

Response to Arguments

Applicant's remarks traversing the rejection of claims 1-25 under obviousness-type double patenting rejection have been fully considered but they are not persuasive.

Applicant argues, "they are not directed to methods for treating cancer".

It is noted that instant claims are directed to a method for preventing or treating toxicity due to pyrimidine nucleoside analog not to a method for treating cancer.

Applicant's claims are broadly directed to the use of a pyrimidine nucleoside in the instant method.

The use of a pyrimidine nucleoside would be obvious to one skilled in this art in view of the prior arts of record. In the instant case, the use of a pyrimidine nucleoside in a method for preventing or treating toxicity due to pyrimidine nucleoside analog, would be considered an inherent property of a pyrimidine nucleoside which can be used for the treatment of cancerous diseases disclosed in the prior art, absent any clear and convincing evidence and/or arguments to the contrary.

35 U.S.C. 112, first paragraph rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph of record, because the specification, while enabling effects of uridine and cytidine derivatives such as triacetyluridine (tau); octanoyl uridine; diacetyldeoxycytidine; and palmtoyldeoxycytidine (specification: Examples, pages 60-106), does not reasonably provide enablement for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal a pharmaceutically effective amount of any acylated derivative of a non-methylated pyrimidine nucleoside. The selection of compounds of an acylated derivative of a non-methylated pyrimidine nucleoside is too broad as the compounds disclosed in Examples, pages 60-106. In the absence of which of an acylated derivative of a non-methylated pyrimidine nucleoside of claim 1 and in the absence of data disclosing the effectiveness of an acylated derivative of a non-methylated pyrimidine nucleoside of claim 1 for preventing or treating toxicity in an animal, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors regarding undue experimentation have been summarized in *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

(1) The nature of the invention;

(2) The state of the prior art;

(3) The predictability or lack thereof in the art;

(4) The amount of direction or guidance present;

(5) The presence or absence of working examples;

(6) The breadth of the claims;

(7) The quantity of experimentation needed; and

(8) The relative skill of those in the art.

THE NATURE OF THE INVENTION

The nature of the invention in claims 1-25 is a method for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside of claim 1.

THE STATE OF THE PRIOR ART

The instant claimed a method for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside. The following references are cited to show the state of the prior art:

Martin et al., Cancer Res., 1982.

Sommadossi et al. Antimicrobial Agents and Chemotherapy, 1988.

(the prior art references are provided in the Office Action dated 2/23/2004).

Martin et al. discloses that administering exogenous uridine can reduce the toxicity of 5-FU and actually "rescue" mice from toxic dose of 5-FU.

Sommadossi et al. also discloses that uridine administration can reduce the toxicity of a pyrimidine nucleoside analog, AZT.

THE PREDICTABILITY OR LACK THEREOF IN THE ART

There would be little predictability in the art of which modifications may be made to an acylated derivative of a non-methylated pyrimidine nucleoside, which would retain its capability to prevent or treat toxicity due to a pyrimidine nucleoside analog comprising administering to an animal. The nature of the pharmaceutical arts is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. In the absence of which Markush groups of the acylated derivative of a non-methylated pyrimidine nucleoside depicted in claim 1 are being effective for the said prevention or treatment, there is no umbrella coverage springing forth from the claimed compounds for the said method.

THE AMOUNT OF DIRECTION OR GUIDANCE PRESENT

The acylated derivative of a non-methylated pyrimidine nucleoside of claim 1 may encompass a great number of compounds having various Markush groups, however, without some guidance as to what specific changes may be made to the instant compound effective for the said treatment, there would be little predictability in making and/or using such compounds. For example, there is no guidance as to which Markush groups may be selected to the specific compound that would retain its capability to prevent or treat toxicity due to a pyrimidine nucleoside analog comprising administering to an animal. One skilled in the art would not expect any modifications of the instant compound, which is effective for the said method.

THE PRESENCE OR ABSENCE OF WORKING EXAMPLES

The working Examples (pages 60-106) disclose the oral administration of TAU, Oct-U, DadC and PdC to ameliorate hematologic toxicity of 5-FU in mice.

BREATH OF THE CLAIMS

The breadth of the claims is that a method for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside.

THE QUANTITY OF EXPERIMENTATION NEEDED

The quantity of experimentation needed is undue experimentation. One skill in the art would need to determine what listed compounds from a broadly claimed acylated derivative of a non-methylated pyrimidine nucleoside of claim 1 would be effective to use in a method for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside.

THE LEVEL OF SKILL IN THE ART

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity **in an animal**. Thus the specification fails to provide sufficient support of the broad use of the acylated derivative of a non-methylated pyrimidine nucleoside of claim 1 because no specific

compound is provided. As a result necessitating one of skill to perform an exhaustive search for which compound can be prepared in order to practice the claimed invention.

Genentech Inc. v Novo Nordish A/S (CA FC) 42 USPQ 2d 1001, states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p] atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which compound out of a broadly claimed acylated derivative of a non-methylated pyrimidine nucleoside of claim 1 is effective in the method encompassed in the instant claims, with no assurance of success.

Rejection Maintained

Applicant's arguments filed on 09/21/06 traversing the rejection of claims 1-25 under 35 U.S.C. 112, first paragraph have been fully considered but they are not persuasive.

Response to Arguments

Applicants argue that "This is not sufficient reasoning to shift the burden to the applicant to address this ground of rejection".

The absence of specific disclosures or the correlation of data to support applicant's assertions, invites the skilled artisan to engage in undue experimentation.

The claimed invention while being enabling effects of uridine and cytidine derivatives such as triacetyluridine (tau); octanoyl uridine; diacetyldeoxycytidine; and palmtoyldeoxycytidine (specification: Examples, pages 60-106), does not reasonably provide enablement for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside. The specification is silent on the activity of any acylated derivative of a non-methylated pyrimidine nucleoside effective in a method for preventing or treating toxicity due to a pyrimidine nucleoside.

2. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Devesh Khare whose telephone number is (571)272-0653. The examiner can normally be reached on Monday to Friday from 8:00 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang, Supervisory Patent Examiner, Art Unit 1623 can be reached at

(571)272-0627. The official fax phone numbers for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Devesh Khare, Ph.D.,J.D.
Art Unit 1623
November 27, 2006

11/27/06
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